DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Seattle District
Pacific Region
22201 23rd Drive SE
Bothell, WA 98021-4421

Telephone: 425-486-8788
FAX: 425-483-4996

August 9, 2006

VIA CERTIFIED MAIL
RETURN RECEIPT REQUESTED

In reply refer to Warning Letter SEA 06-41

Benjamin S. Paschall, CEO
Pascal Company, Inc.
P.O. Box 1478
Bellevue, Washington 98009-1478

WARNING LETTER

Dear Mr. Paschall:

During an inspection of your drug manufacturing facility conducted March 28, 2006, through April 18, 2006, FDA investigators documented significant deviations from the current good manufacturing practice (CGMP) regulations (Title 21, Code of Federal Regulations, Parts 210 and 211). Such deviations cause your prescription and over-the-counter dental drug products to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. § 351(a)(2)(B)] as follows:

1) **There is a failure to establish and follow appropriate written procedures designed to prevent objectionable microorganisms in drug products not required to be sterile [21 C.F.R. § 211.113(a)].** For example,

- Your firm has not established and followed appropriate written procedures to prevent objectionable microorganisms in your drug products as evidenced by numerous batches of your NeutraGard® Fluoride Rinse products testing positive for either (1) *Pseudomonas aeruginosa*, a Gram-negative bacterium, or (2) *Burkholderia cepacia*, a Gram-negative bacterium. As a result, you have recalled all lots of NeutraGard 0.05% Rinse and NeutraGard Plus Rinse distributed since 2001.
- Your firm failed to follow your system sanitization procedures (for water purification) despite numerous water samples demonstrating high microbial counts.

2) **There is a failure of the equipment used in the manufacture, processing, packing, or holding of a drug product to be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance (21 C.F.R. § 211.63).** For example,

- Your firm has not properly validated either (1) the plant purified water system or (2) the production laboratory water system. Proper validation should include the following elements: (1) a description of the water system along with a print (i.e., drawing that shows all equipment in the system from the water feed to points of use); (2) operational parameters (including cleaning and sanitization procedures); and (3) a demonstration (with appropriate sampling plans) that the water system will consistently produce the desired water quality when operated in conformance with established SOPs over a long period of time.

3) **There is a failure to follow written procedures for the cleaning and maintenance of equipment used in the manufacture, processing, packing, and holding of drug products [21 C.F.R. § 211.67(b)].** For example,

- Contrary to SOP, your firm failed to replace the [redacted] micron filter in the purified water system when pressure readings were consistently documented as "0" units (psi) since October 2004.

4) **There is a failure of the quality control unit to approve or reject all procedures or specifications impacting the identity, strength, quality, and purity of the drug product [21 C.F.R. § 211.22(c)].** For example,

- Your firm increased the antimicrobial agent in several flavors of your fluoride gel without a formal review and approval by the quality control unit.
- Your firm added [redacted] more resin beds to the plant purified water system without a formal review and approval by the quality control unit.
- Your firm decreased the amount of EDTA in two fluoride rinse products in July 2003 without a formal review and approval by the quality control unit.

5) **There is a failure to have written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess [21 C.F.R. § 211.100(a)].** For example,

- Your firm has not completed the process validation for the production of your drug products.

6) **There is a failure to have a written testing program to include reliable, meaningful, and specific test methods designed to assess the stability characteristics of drugs products [21 C.F.R. § 211.166(a)].** For example,

- Your firm has failed to assess the stability of the preservatives in your drug product. Consequently, there is no assurance that the drug product will be adequately preserved throughout the expiry period.
- Additionally, your firm fails to have a meaningful test method for evaluating the potential degradation of Racemistat (Racemic Epinepherine HCL 8% solution).

7) **There is a failure to thoroughly investigate the failure of a batch or any of its components to meet any of its specifications whether or not the batch has already been distributed [21 C.F.R. § 211.192].** For example,

- Your firm's investigations into stability failures do not include (1) the actual failing result in the investigation report or (2) the impact of the stability failure on already distributed lots.

8) **There is a failure to follow written procedures describing the handling of all written and oral complaints regarding a drug product [21 C.F.R. § 211.198].** For example,

- Your firm failed to investigate a complaint to determine the origin of black flakes in a drug product. Your preventative action plan states only that the product is undergoing reformulation to address the issue. Your firm did not determine the impact of these black flakes on the identity, strength, quality, and purity of the drug product.

We do not intend the above violations to be an all-inclusive list of the deficiencies at your facility. In addition to the egregious violations cited above, the current inspection documented (1) a facility in need of significant repair and sanitization, (2) incomplete master product and control records, (3) component control concerns, (4) product labeling concerns, and (5) equipment calibration concerns.

It is your responsibility to assure adherence with each requirement of the CGMP regulations and the Federal Food, Drug, and Cosmetic Act. For regulatory and scientific guidance, e.g., Guide to Inspections of High Purity Water Systems, at http://www.fda.gov/ora/inspect_ref/igs/high.html, please refer to FDA's website, at http://www.fda.gov/cder/guidance/index.htm.

Federal agencies are advised of the issuance of all warning letters about drugs so that they may consider this information when considering award of contracts. Additionally, the FDA may not approve any pending drug applications or export approval requests until your firm effects systemic corrections to the above violations.

You should take prompt action to correct these violations. Failure to correct these violations promptly may result in regulatory action by the FDA without further notice. These actions include, but are not limited to, seizure and/or injunction.

We acknowledge receipt of a written response dated May 4, 2006, from Vincent M. Tentarelli, Quality Assurance Manager for Pascal Co., Inc., which responds to the Form FDA 483 issued at the conclusion of the inspection. Our review finds that the response does not adequately address the problems specified on the Form FDA 483. For example, your response:

- Describes in general terms that corrective measures will be undertaken by your firm such as receiving a quote for modifying the water system and renovating the fluoride rinse room, repairing and replacing equipment, soliciting bids for building repairs, revising existing procedures, investigating new methods, amongst other general promises for

correction. Your firm does not provide specific corrective actions with expected dates of completion.

- Assures the FDA "... that all products manufactured in the interim will be protected from any external source of contamination and produced in a manner that will not adversely affect its identity, strength, quality and purity..." However, your response does not provide any specific explanation or documentation to support this statement.

Because of these deficiencies, your response letter does not provide adequate assurance that similar violations will not reoccur in the future.

Please notify this office immediately to schedule a meeting with the District Office within five (5) working days of the receipt of this letter.

At the meeting, your firm should be prepared to discuss the specific steps your firm has taken to correct these violations, including a detailed explanation of each step taken to ensure that these types of violations do not reoccur. Please bring the necessary documentation to demonstrate that your firm has adequately effected systemic corrections to the above violations. Your reply should be sent to the Food and Drug Administration, Attention: Lisa Althar, Compliance Officer, 22201 23rd Drive SE, Bothell, Washington 98021-4421.

Sincerely,

Charles M. Breen
District Director

cc: David E. Watton, President
Pascal Company, Inc.
P.O. Box 1478
Bellevue, Washington 98009-1478